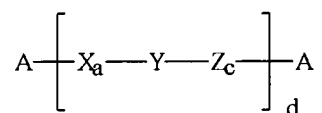


# IN THE CLAIMS

Please delete all prior lists of claims in the application and insert the following list of claims:

1-3. (CANCELED)

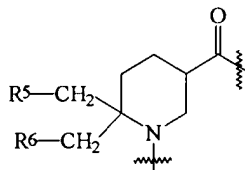
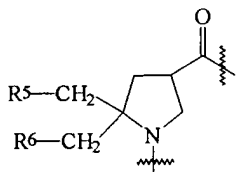
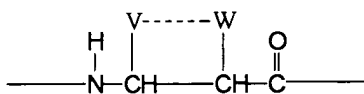
4. (PREVIOUSLY PRESENTED) An isolated, unnatural polypeptide compound of formula:

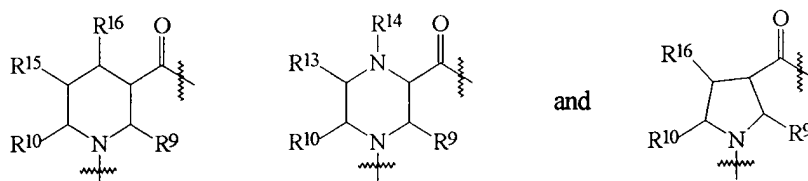


wherein:

each X and each Z is independently variable and is selected from the group consisting of  $\alpha$ -amino acid residues,  $\beta$ -amino acid residues, and  $\gamma$ -amino acid residues, provided that at least one X or Z comprises an  $\alpha$ -amino acid residue and at least another two of X or Z comprise two cyclically-constrained  $\beta$ -amino acid residues; and

wherein each cyclically-constrained  $\beta$ -amino acid residue is independently selected from the group consisting of:





wherein V and W are combined, together with the carbon atoms to which they are bonded, and independently define a substituted or unsubstituted, monocyclic or bicyclic C<sub>3</sub>-C<sub>10</sub> cycloalkyl, cycloalkenyl or heterocyclic ring having one or more N, O or S atom(s) as the heteroatom(s);

the substituents on carbon atoms of the rings being independently selected from the group consisting of linear, branched, or cyclic C<sub>1</sub>-C<sub>6</sub>-alkyl, alkenyl, alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C<sub>1</sub>-C<sub>6</sub>-alkyl, mono- or bicyclic heteroaryl-C<sub>1</sub>-C<sub>6</sub>-alkyl, and the substituents listed above for V and W when V and W are not combined;

the substituents on nitrogen heteroatoms of the rings being independently selected from the group consisting of hydrogen, monocyclic or bicyclic C<sub>1</sub>-C<sub>10</sub>-alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C<sub>1</sub>-C<sub>6</sub>-alkyl, mono- or bicyclic heteroaryl-C<sub>1</sub>-C<sub>6</sub>-alkyl, -S(=O)<sub>2</sub>-R<sup>17</sup>, -C(=O)-R<sup>17</sup>, -S(=O)<sub>2</sub>-(CH<sub>2</sub>)<sub>n+1</sub>-R<sup>18</sup>, and -C(=O)-(CH<sub>2</sub>)<sub>n</sub>-R<sup>18</sup>, where n = 1 to 6;

wherein R<sup>17</sup> is independently selected from the group consisting of hydrogen, monocyclic or bicyclic C<sub>1</sub>-C<sub>10</sub>-alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C<sub>1</sub>-C<sub>6</sub>-alkyl, mono- or bicyclic heteroaryl-C<sub>1</sub>-C<sub>6</sub>-alkyl; and

wherein R<sup>18</sup> is independently selected from the group consisting of hydroxy, linear, branched, or cyclic C<sub>1</sub>-C<sub>6</sub>-alkyl, alkenyl, or alkynyl; mono-

or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C<sub>1</sub>-C<sub>6</sub>-alkyl; mono- or bicyclic heteroaryl-C<sub>1</sub>-C<sub>6</sub>-alkyl; C<sub>1</sub>-C<sub>6</sub>-alkyloxy, aryloxy, heteroaryloxy, thio, C<sub>1</sub>-C<sub>6</sub>-alkylthio, C<sub>1</sub>-C<sub>6</sub>-alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub>-alkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, amino, mono- or di-C<sub>1</sub>-C<sub>6</sub>-alkylamino, mono- or diarylamino, mono- or diheteroarylamino, N-alkyl-N-arylamino, N-alkyl-N-heteroarylamino, N-aryl-N-heteroarylamino, aryl-C<sub>1</sub>-C<sub>6</sub>-alkylamino, carboxylic acid, carboxamide, mono- or di-C<sub>1</sub>-C<sub>6</sub>-alkylcarboxamide, mono- or diarylcarboxamide, mono- or diheteroarylcarboxamide, N-alkyl-N-arylcarboxamide, N-alkyl-N-heteroarylcarboxamide, N-aryl-N-heteroarylcarboxamide, sulfonic acid, sulfonamide, mono- or di-C<sub>1</sub>-C<sub>6</sub>-alkylsulfonamide, mono- or diarylsulfonamide, mono- or diheteroarylsulfonamide, N-alkyl-N-arylsulfonamide, N-alkyl-N-heteroarylsulfonamide, N-aryl-N-heteroarylsulfonamide, urea; mono- di- or tri-substituted urea, wherein the substituent(s) is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub>-alkyl, aryl, heteroaryl; O-alkylurethane, O-arylurethane, and O-heteroarylurethane; and

wherein R<sup>5</sup> and R<sup>6</sup> are independently selected from the group consisting of hydrogen, hydroxy, linear, branched, or cyclic C<sub>1</sub>-C<sub>16</sub>-alkyl, alkenyl, or alkynyl; mono- or di- C<sub>1</sub>-C<sub>16</sub> alkylamino; mono- or bicyclic aryl; mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C<sub>1</sub>-C<sub>16</sub>-alkyl; mono- or bicyclic heteroaryl-C<sub>1</sub>-C<sub>16</sub>-alkyl; -(CH<sub>2</sub>)<sub>0-6</sub>-OR<sup>7</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-SR<sup>7</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-S(=O)-CH<sub>2</sub>-R<sup>7</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-S(=O)<sub>2</sub>-CH<sub>2</sub>-R<sup>7</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-NR<sup>7</sup>R<sup>7</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-NHC(=O)R<sup>7</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-NHS(=O)<sub>2</sub>-CH<sub>2</sub>-R<sup>7</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-C(=O)-OH, -(CH<sub>2</sub>)<sub>0-6</sub>-C(=O)-OR<sup>7</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-C(=O)-NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>0-6</sub>-C(=O)-NHR<sup>7</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-C(=O)-N(R<sup>7</sup>)<sub>2</sub>, -(CH<sub>2</sub>)<sub>0-6</sub>-O-(CH<sub>2</sub>)<sub>2-6</sub>-R<sup>8</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-S-(CH<sub>2</sub>)<sub>2-6</sub>-R<sup>8</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-S(=O)-(CH<sub>2</sub>)<sub>2-6</sub>-R<sup>8</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-S(=O)<sub>2</sub>-(CH<sub>2</sub>)<sub>2-6</sub>-R<sup>8</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-NH-

$(\text{CH}_2)_{2-6}\text{-R}^8$ ,  $-(\text{CH}_2)_{0-6}\text{-N-}\{(\text{CH}_2)_{2-6}\text{-R}^8\}_2$ ,  $-(\text{CH}_2)_{0-6}\text{-NHC(=O)-}(\text{CH}_2)_{2-6}\text{-R}^8$ , and  $-(\text{CH}_2)_{0-6}\text{-NHS(=O)}_2\text{-}(\text{CH}_2)_{2-6}\text{-R}^8$ ; wherein

$\text{R}^7$  is independently selected from the group consisting of hydrogen,  $\text{C}_1\text{-C}_6\text{-alkyl}$ , alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl- $\text{C}_1\text{-C}_6\text{-alkyl}$ , mono- or bicyclic heteroaryl- $\text{C}_1\text{-C}_6\text{-alkyl}$ ; and

$\text{R}^8$  is selected from the group consisting of hydroxy,  $\text{C}_1\text{-C}_6\text{-alkyloxy}$ , aryloxy, heteroaryloxy, thio,  $\text{C}_1\text{-C}_6\text{-alkylthio}$ ,  $\text{C}_1\text{-C}_6\text{-alkylsulfinyl}$ ,  $\text{C}_1\text{-C}_6\text{-alkylsulfonyl}$ , arylthio, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, amino, mono- or di- $\text{C}_1\text{-C}_6\text{-alkylamino}$ , mono- or diarylamino, mono- or diheteroaryl amino, N-alkyl-N-arylamino, N-alkyl-N-heteroaryl amino, N-aryl-N-heteroaryl amino, aryl- $\text{C}_1\text{-C}_6\text{-alkylamino}$ , carboxylic acid, carboxamide, mono- or di- $\text{C}_1\text{-C}_6\text{-alkylcarboxamide}$ , mono- or diarylcarboxamide, mono- or diheteroarylcarboxamide, N-alkyl-N-arylcarboxamide, N-alkyl-N-heteroarylcarboxamide, N-aryl-N-heteroarylcarboxamide, sulfonic acid, sulfonamide, mono- or di- $\text{C}_1\text{-C}_6\text{-alkylsulfonamide}$ , mono- or diarylsulfonamide, mono- or diheteroarylsulfonamide, N-alkyl-N-arylsulfonamide, N-alkyl-N-heteroarylsulfonamide, N-aryl-N-heteroarylsulfonamide, urea; mono- di- or tri-substituted urea, wherein the substituent(s) is selected from the group consisting of  $\text{C}_1\text{-C}_6\text{-alkyl}$ , aryl, heteroaryl; O-alkylurethane, O-arylurethane, and O-heteroarylurethane; and wherein  $\text{R}^9$ ,  $\text{R}^{10}$ , and  $\text{R}^{13}$  are independently selected from the group consisting of hydrogen, linear, branched, or cyclic  $\text{C}_1\text{-C}_6\text{-alkyl}$ , alkenyl, or alkynyl; mono- or di-  $\text{C}_1\text{-C}_6\text{-alkylamino}$ , mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl- $\text{C}_1\text{-C}_6\text{-alkyl}$ , mono- or bicyclic heteroaryl- $\text{C}_1\text{-C}_6\text{-alkyl}$ ,  $-(\text{CH}_2)_{1-6}\text{-OR}^{11}$ ,  $-(\text{CH}_2)_{1-6}\text{-SR}^{11}$ ,  $-(\text{CH}_2)_{1-6}\text{-S(=O)-CH}_2\text{-R}^{11}$ ,  $-(\text{CH}_2)_{1-6}\text{-S(=O)}_2\text{-CH}_2\text{-R}^{11}$ ,  $-(\text{CH}_2)_{1-6}\text{-NR}^{11}\text{R}^{11}$ ,  $-(\text{CH}_2)_{1-6}\text{-NHC(=O)R}^{11}$ ,  $-(\text{CH}_2)_{1-6}\text{-NHS(=O)}_2\text{-CH}_2\text{-R}^{11}$ ,  $-(\text{CH}_2)_{0-6}\text{-C(=O)-OH}$ ,

$-(CH_2)_{0-6}-C(=O)-OR^{11}$ ,  $-(CH_2)_{0-6}-C(=O)-NH_2$ ,  $-(CH_2)_{0-6}-C(=O)-NHR^{11}$ ,  $-(CH_2)_{0-6}-C(=O)-N(R^{11})_2$ ,  $-(CH_2)_{1-6}-O-(CH_2)_{2-6}-R^{12}$ ,  $-(CH_2)_{1-6}-S-(CH_2)_{2-6}-R^{12}$ ,  $-(CH_2)_{1-6}-S(=O)-(CH_2)_{2-6}-R^{12}$ ,  $-(CH_2)_{1-6}-S(=O)_2-(CH_2)_{2-6}-R^{12}$ ,  $-(CH_2)_{1-6}-NH-(CH_2)_{2-6}-R^{12}$ ,  $-(CH_2)_{1-6}-N-\{(CH_2)_{2-6}-R^{12}\}_2$ ,  $-(CH_2)_{1-6}-NHC(=O)-(CH_2)_{2-6}-R^{12}$ , and  $-(CH_2)_{1-6}-NHS(=O)_2-(CH_2)_{2-6}-R^{12}$ ; wherein

$R^{11}$  is independently selected from the group consisting of hydrogen,  $C_1$ - $C_6$ -alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl- $C_1$ - $C_6$ -alkyl, mono- or bicyclic heteroaryl- $C_1$ - $C_6$ -alkyl; and

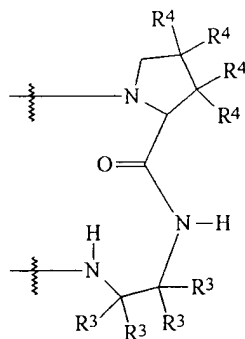
$R^{12}$  is selected from the group consisting of hydroxy,  $C_1$ - $C_6$ -alkyloxy, aryloxy, heteroaryloxy, thio,  $C_1$ - $C_6$ -alkylthio,  $C_1$ - $C_6$ -alkylsulfinyl,  $C_1$ - $C_6$ -alkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, amino, mono- or di- $C_1$ - $C_6$ -alkylamino, mono- or diarylamino, mono- or diheteroarylamino, N-alkyl-N-aryl-amino, N-alkyl-N-heteroaryl-amino, N-aryl-N-heteroaryl-amino, aryl- $C_1$ - $C_6$ -alkylamino, carboxylic acid, carboxamide, mono- or di- $C_1$ - $C_6$ -alkylcarboxamide, mono- or diarylcarboxamide, mono- or diheteroarylcarboxamide, N-alkyl-N-arylcarboxamide, N-alkyl-N-heteroarylcarboxamide, N-aryl-N-heteroarylcarboxamide, sulfonic acid, sulfonamide, mono- or di- $C_1$ - $C_6$ -alkylsulfonamide, mono- or diarylsulfonamide, mono- or diheteroarylsulfonamide, N-alkyl-N-aryl-sulfonamide, N-alkyl-N-heteroarylsulfonamide, N-aryl-N-heteroarylsulfonamide, urea; mono- di- or tri-substituted urea, wherein the substituent(s) is selected from the group consisting of  $C_1$ - $C_6$ -alkyl, aryl, heteroaryl; O-alkylurethane, O-arylurethane, and O-heteroarylurethane;

$R^{14}$  is selected from the group consisting of hydrogen, linear, branched, or cyclic  $C_1$ - $C_6$ -alkyl, alkenyl, or alkynyl; mono- or di-  $C_1$ - $C_6$  alkylamino, mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl- $C_1$ - $C_6$ -alkyl, mono- or bicyclic heteroaryl- $C_1$ -

C<sub>6</sub>-alkyl, -S(=O)<sub>2</sub>-(CH<sub>2</sub>)<sub>1-6</sub>-R<sup>11</sup>, -C(=O)R<sup>11</sup>, -S(=O)<sub>2</sub>-(CH<sub>2</sub>)<sub>2-6</sub>R<sup>12</sup>, and -C(=O)-(CH<sub>2</sub>)<sub>1-6</sub>-R<sup>12</sup>; wherein R<sup>11</sup> and R<sup>12</sup> are as defined above;

R<sup>15</sup> and R<sup>16</sup> are selected from the group listed above for R<sup>9</sup>, R<sup>10</sup>, and R<sup>13</sup>, and are further selected from the group consisting of hydroxy, C<sub>1</sub>-C<sub>6</sub>-alkyloxy, aryloxy, heteroaryloxy, thio, C<sub>1</sub>-C<sub>6</sub>-alkylthio, C<sub>1</sub>-C<sub>6</sub>-alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub>-alkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, amino, mono- or di-C<sub>1</sub>-C<sub>6</sub>-alkylamino, mono- or diarylamino, mono- or diheteroarylamino, N-alkyl-N-arylamino, N-alkyl-N-heteroarylamino, N-aryl-N-heteroarylamino, aryl-C<sub>1</sub>-C<sub>6</sub>-alkylamino, carboxylic acid, carboxamide, mono- or di-C<sub>1</sub>-C<sub>6</sub>-alkylcarboxamide, mono- or diarylcarboxamide, mono- or diheteroarylcarboxamide, N-alkyl-N-arylcarboxamide, N-alkyl-N-heteroarylcarboxamide, N-aryl-N-heteroarylcarboxamide, sulfonic acid, sulfonamide, mono- or di-C<sub>1</sub>-C<sub>6</sub>-alkylsulfonamide, mono- or diarylsulfonamide, mono- or diheteroarylsulfonamide, N-alkyl-N-arylsulfonamide, N-alkyl-N-heteroarylsulfonamide, N-aryl-N-heteroarylsulfonamide, urea; mono- di- or tri-substituted urea, wherein the substituent(s) is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub>-alkyl, aryl, heteroaryl; O-alkylurethane, O-arylurethane, and O-heteroarylurethane; and each "Y" is independently variable and is a single bond or a reverse-turn moiety; and each "A" is independently selected from the group consisting of hydrogen, hydroxy, an amino-terminus protecting group, and a carboxy-terminus protecting group; and each "a," "c," and "d" is an independently variable positive integer, and wherein "a" + "c" > 3; and salts thereof.

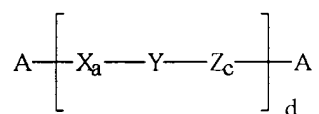
5. (ORIGINAL) The compound of Claim 4, wherein each Y is a single bond or a reverse turn moiety independently selected from group consisting of a prolyl-glycolic acid residue, a di-nipecotic acid residue, or a compound of the following formula:



where each  $R^3$  is independently variable and is selected from the group consisting of hydrogen, linear, branched, or cyclic  $C_1$ - $C_6$ -alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl- $C_1$ - $C_6$ -alkyl, and mono- or bicyclic heteroaryl- $C_1$ - $C_6$ -alkyl; and

where each  $R^4$  is selected from the group consisting of hydroxy, linear, branched, or cyclic  $C_1$ - $C_6$ -alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl- $C_1$ - $C_6$ -alkyl; mono- or bicyclic heteroaryl- $C_1$ - $C_6$ -alkyl;  $C_1$ - $C_6$ -alkyloxy, aryloxy, heteroaryloxy, thio,  $C_1$ - $C_6$ -alkylthio,  $C_1$ - $C_6$ -alkylsulfinyl,  $C_1$ - $C_6$ -alkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, amino, mono- or di- $C_1$ - $C_6$ -alkylamino, mono- or diarylamino, mono- or diheteroarylamino, N-alkyl-N-arylamino, N-alkyl-N-heteroarylamino, N-aryl-N-heteroarylamino, aryl- $C_1$ - $C_6$ -alkylamino, carboxylic acid, carboxamide, mono- or di- $C_1$ - $C_6$ -alkylcarboxamide, mono- or diarylcarboxamide, mono- or diheteroarylcarboxamide, N-alkyl-N-arylcarboxamide, N-alkyl-N-heteroarylcarboxamide, N-aryl-N-heteroarylcarboxamide, sulfonic acid, sulfonamide, mono- or di- $C_1$ - $C_6$ -alkylsulfonamide, mono- or diarylsulfonamide, mono- or diheteroarylsulfonamide, N-alkyl-N-arylsulfonamide, N-alkyl-N-heteroarylsulfonamide, N-aryl-N-heteroarylsulfonamide, urea; mono- di- or tri-substituted urea, wherein the substituent(s) is selected from the group consisting of  $C_1$ - $C_6$ -alkyl, aryl, heteroaryl; O-alkylurethane, O-arylurethane, and O-heteroarylurethane.

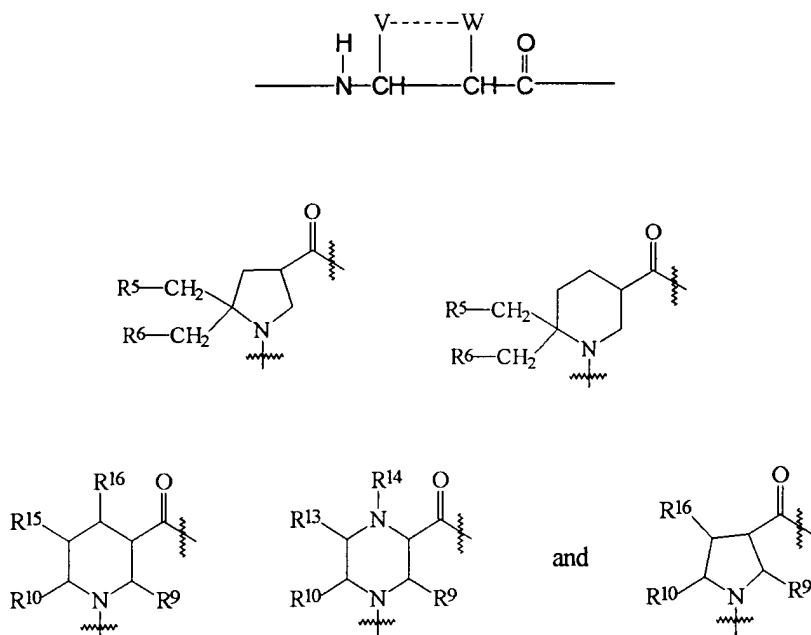
6. (PREVIOUSLY PRESENTED) An isolated, unnatural polypeptide compound of formula:



wherein:

each X and each Z is independently variable and is selected from the group consisting of  $\alpha$ -amino acid residues,  $\beta$ -amino acid residues, and  $\gamma$ -amino acid residues, provided that at least one X or Z is an  $\alpha$ -amino acid residue and at least another two of X or Z comprise two cyclically-constrained residues, the two cyclically-constrained residues comprising cyclically-constrained  $\beta$ -amino acid residues or cyclically-constrained  $\gamma$ -amino acid residues, or one cyclically-constrained  $\beta$ -amino acid residue and one cyclically-constrained  $\gamma$ -amino acid residue; and

wherein the cyclically-constrained  $\beta$ -amino acid residues are selected from the group consisting of:





wherein V and W are combined, together with the carbon atoms to which they are bonded, and independently define a substituted or unsubstituted, monocyclic or bicyclic C<sub>3</sub>-C<sub>10</sub> cycloalkyl, cycloalkenyl or heterocyclic ring having one or more N, O or S atom(s) as the heteroatom(s);

the substituents on carbon atoms of the rings being independently selected from the group consisting of linear, branched, or cyclic C<sub>1</sub>-C<sub>6</sub>-alkyl, alkenyl, alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C<sub>1</sub>-C<sub>6</sub>-alkyl, mono- or bicyclic heteroaryl-C<sub>1</sub>-C<sub>6</sub>-alkyl, and the substituents listed above for V and W when V and W are not combined;

the substituents on nitrogen heteroatoms of the rings being independently selected from the group consisting of hydrogen, monocyclic or bicyclic C<sub>1</sub>-C<sub>10</sub>-alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C<sub>1</sub>-C<sub>6</sub>-alkyl, mono- or bicyclic heteroaryl-C<sub>1</sub>-C<sub>6</sub>-alkyl, -S(=O)<sub>2</sub>-R<sup>17</sup>, -C(=O)-R<sup>17</sup>, -S(=O)<sub>2</sub>-(CH<sub>2</sub>)<sub>n+1</sub>-R<sup>18</sup>, and -C(=O)-(CH<sub>2</sub>)<sub>n</sub>-R<sup>18</sup>, where n = 1 to 6;

wherein R<sup>17</sup> is independently selected from the group consisting of hydrogen, monocyclic or bicyclic C<sub>1</sub>-C<sub>10</sub>-alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C<sub>1</sub>-C<sub>6</sub>-alkyl, mono- or bicyclic heteroaryl-C<sub>1</sub>-C<sub>6</sub>-alkyl; and

wherein R<sup>18</sup> is independently selected from the group consisting of hydroxy, linear, branched, or cyclic C<sub>1</sub>-C<sub>6</sub>-alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C<sub>1</sub>-C<sub>6</sub>-alkyl; mono- or bicyclic heteroaryl-C<sub>1</sub>-C<sub>6</sub>-alkyl; C<sub>1</sub>-C<sub>6</sub>-alkyloxy, aryloxy, heteroaryloxy, thio, C<sub>1</sub>-C<sub>6</sub>-alkylthio, C<sub>1</sub>-C<sub>6</sub>-alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub>-alkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, amino, mono- or di-C<sub>1</sub>-C<sub>6</sub>-alkylamino, mono- or

diaryl-amino, mono- or diheteroaryl-amino, N-alkyl-N-aryl-amino, N-alkyl-N-heteroaryl-amino, N-aryl-N-heteroaryl-amino, aryl-C<sub>1</sub>-C<sub>6</sub>-alkyl-amino, carboxylic acid, carboxamide, mono- or di-C<sub>1</sub>-C<sub>6</sub>-alkyl-carboxamide, mono- or diaryl-carboxamide, mono- or diheteroaryl-carboxamide, N-alkyl-N-aryl-carboxamide, N-alkyl-N-heteroaryl-carboxamide, N-aryl-N-heteroaryl-carboxamide, sulfonic acid, sulfonamide, mono- or di-C<sub>1</sub>-C<sub>6</sub>-alkyl-sulfonamide, mono- or diaryl-sulfonamide, mono- or diheteroaryl-sulfonamide, N-alkyl-N-aryl-sulfonamide, N-alkyl-N-heteroaryl-sulfonamide, N-aryl-N-heteroaryl-sulfonamide, urea; mono- di- or tri-substituted urea, wherein the substituent(s) is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub>-alkyl, aryl, heteroaryl; O-alkylurethane, O-arylurethane, and O-heteroarylurethane; and

wherein R<sup>5</sup> and R<sup>6</sup> are independently selected from the group consisting of hydrogen, hydroxy, linear, branched, or cyclic C<sub>1</sub>-C<sub>16</sub>-alkyl, alkenyl, or alkynyl; mono- or di- C<sub>1</sub>-C<sub>16</sub> alkyl-amino; mono- or bicyclic aryl; mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C<sub>1</sub>-C<sub>16</sub>-alkyl; mono- or bicyclic heteroaryl-C<sub>1</sub>-C<sub>16</sub>-alkyl; -(CH<sub>2</sub>)<sub>0-6</sub>-OR<sup>7</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-SR<sup>7</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-S(=O)-CH<sub>2</sub>-R<sup>7</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-S(=O)<sub>2</sub>-CH<sub>2</sub>-R<sup>7</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-NR<sup>7</sup>R<sup>7</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-NHC(=O)R<sup>7</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-NHS(=O)<sub>2</sub>-CH<sub>2</sub>-R<sup>7</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-C(=O)-OH, -(CH<sub>2</sub>)<sub>0-6</sub>-C(=O)-OR<sup>7</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-C(=O)-NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>0-6</sub>-C(=O)-NHR<sup>7</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-C(=O)-N(R<sup>7</sup>)<sub>2</sub>, -(CH<sub>2</sub>)<sub>0-6</sub>-O-(CH<sub>2</sub>)<sub>2-6</sub>-R<sup>8</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-S-(CH<sub>2</sub>)<sub>2-6</sub>-R<sup>8</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-S(=O)-(CH<sub>2</sub>)<sub>2-6</sub>-R<sup>8</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-S(=O)<sub>2</sub>-(CH<sub>2</sub>)<sub>2-6</sub>-R<sup>8</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-NH-(CH<sub>2</sub>)<sub>2-6</sub>-R<sup>8</sup>, -(CH<sub>2</sub>)<sub>0-6</sub>-N-{(CH<sub>2</sub>)<sub>2-6</sub>-R<sup>8</sup>}<sub>2</sub>, -(CH<sub>2</sub>)<sub>0-6</sub>-NHC(=O)-(CH<sub>2</sub>)<sub>2-6</sub>-R<sup>8</sup>, and -(CH<sub>2</sub>)<sub>0-6</sub>-NHS(=O)<sub>2</sub>-(CH<sub>2</sub>)<sub>2-6</sub>-R<sup>8</sup>; wherein

R<sup>7</sup> is independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub>-alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C<sub>1</sub>-C<sub>6</sub>-alkyl, mono- or bicyclic heteroaryl-C<sub>1</sub>-C<sub>6</sub>-alkyl; and

R<sup>8</sup> is selected from the group consisting of hydroxy, C<sub>1</sub>-C<sub>6</sub>-alkyloxy, aryloxy, heteroaryloxy, thio, C<sub>1</sub>-C<sub>6</sub>-alkylthio, C<sub>1</sub>-C<sub>6</sub>-alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub>-alkylsulfonyl, arylthio,

arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, amino, mono- or di-C<sub>1</sub>-C<sub>6</sub>-alkylamino, mono- or diarylamino, mono- or diheteroarylamino, N-alkyl-N-arylamino, N-alkyl-N-heteroarylamino, N-aryl-N-heteroarylamino, aryl-C<sub>1</sub>-C<sub>6</sub>-alkylamino, carboxylic acid, carboxamide, mono- or di-C<sub>1</sub>-C<sub>6</sub>-alkylcarboxamide, mono- or diarylcarboxamide, mono- or diheteroarylcarboxamide, N-alkyl-N-arylcarboxamide, N-alkyl-N-heteroarylcarboxamide, N-aryl-N-heteroarylcarboxamide, sulfonic acid, sulfonamide, mono- or di-C<sub>1</sub>-C<sub>6</sub>-alkylsulfonamide, mono- or diarylsulfonamide, mono- or diheteroarylsulfonamide, N-alkyl-N-arylsulfonamide, N-alkyl-N-heteroarylsulfonamide, N-aryl-N-heteroarylsulfonamide, urea; mono- di- or tri-substituted urea, wherein the substituent(s) is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub>-alkyl, aryl, heteroaryl; O-alkylurethane, O-arylurethane, and O-heteroarylurethane;

wherein R<sup>9</sup>, R<sup>10</sup>, and R<sup>13</sup> are independently selected from the group consisting of hydrogen, linear, branched, or cyclic C<sub>1</sub>-C<sub>6</sub>-alkyl, alkenyl, or alkynyl; mono- or di- C<sub>1</sub>-C<sub>6</sub> alkylamino, mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C<sub>1</sub>-C<sub>6</sub>-alkyl, mono- or bicyclic heteroaryl-C<sub>1</sub>-C<sub>6</sub>-alkyl,  $-(CH_2)_{1-6}-OR^{11}$ ,  $-(CH_2)_{1-6}-SR^{11}$ ,  $-(CH_2)_{1-6}-S(=O)-CH_2-R^{11}$ ,  $-(CH_2)_{1-6}-S(=O)_2-CH_2-R^{11}$ ,  $-(CH_2)_{1-6}-NR^{11}R^{11}$ ,  $-(CH_2)_{1-6}-NHC(=O)R^{11}$ ,  $-(CH_2)_{1-6}-NHS(=O)_2-CH_2-R^{11}$ ,  $-(CH_2)_{0-6}-C(=O)-OH$ ,  $-(CH_2)_{0-6}-C(=O)-OR^{11}$ ,  $-(CH_2)_{0-6}-C(=O)-NH_2$ ,  $-(CH_2)_{0-6}-C(=O)-NHR^{11}$ ,  $-(CH_2)_{0-6}-C(=O)-N(R^{11})_2$ ,  $-(CH_2)_{1-6}-O-(CH_2)_{2-6}-R^{12}$ ,  $-(CH_2)_{1-6}-S-(CH_2)_{2-6}-R^{12}$ ,  $-(CH_2)_{1-6}-S(=O)-(CH_2)_{2-6}-R^{12}$ ,  $-(CH_2)_{1-6}-S(=O)_2-(CH_2)_{2-6}-R^{12}$ ,  $-(CH_2)_{1-6}-NH-(CH_2)_{2-6}-R^{12}$ ,  $-(CH_2)_{1-6}-N-\{(CH_2)_{2-6}-R^{12}\}_2$ ,  $-(CH_2)_{1-6}-NHC(=O)-(CH_2)_{2-6}-R^{12}$ , and  $-(CH_2)_{1-6}-NHS(=O)_2-(CH_2)_{2-6}-R^{12}$ ; wherein

R<sup>11</sup> is independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub>-alkyl, alkenyl, or alkynyl; mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C<sub>1</sub>-C<sub>6</sub>-alkyl, mono- or bicyclic heteroaryl-C<sub>1</sub>-C<sub>6</sub>-alkyl; and

R<sup>12</sup> is selected from the group consisting of hydroxy, C<sub>1</sub>-C<sub>6</sub>-alkyloxy, aryloxy, heteroaryloxy, thio, C<sub>1</sub>-C<sub>6</sub>-alkylthio, C<sub>1</sub>-C<sub>6</sub>-alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub>-alkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl,

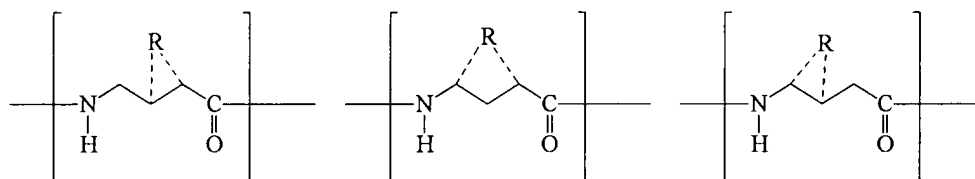
heteroarylsulfonyl, amino, mono- or di-C<sub>1</sub>-C<sub>6</sub>-alkylamino, mono- or diarylamino, mono- or diheteroarylamino, N-alkyl-N-arylamino, N-alkyl-N-heteroarylamino, N-aryl-N-heteroarylamino, aryl-C<sub>1</sub>-C<sub>6</sub>-alkylamino, carboxylic acid, carboxamide, mono- or di-C<sub>1</sub>-C<sub>6</sub>-alkylcarboxamide, mono- or diarylcarboxamide, mono- or diheteroarylcarboxamide, N-alkyl-N-arylcarboxamide, N-alkyl-N-heteroarylcarboxamide, N-aryl-N-heteroarylcarboxamide, sulfonic acid, sulfonamide, mono- or di-C<sub>1</sub>-C<sub>6</sub>-alkylsulfonamide, mono- or diarylsulfonamide, mono- or diheteroarylsulfonamide, N-alkyl-N-arylsulfonamide, N-alkyl-N-heteroarylsulfonamide, N-aryl-N-heteroarylsulfonamide, urea; mono- di- or tri-substituted urea, wherein the substituent(s) is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub>-alkyl, aryl, heteroaryl; O-alkylurethane, O-arylurethane, and O-heteroarylurethane;

R<sup>14</sup> is selected from the group consisting of hydrogen, linear, branched, or cyclic C<sub>1</sub>-C<sub>6</sub>-alkyl, alkenyl, or alkynyl; mono- or di- C<sub>1</sub>-C<sub>6</sub> alkylamino, mono- or bicyclic aryl, mono- or bicyclic heteroaryl having up to 5 heteroatoms selected from N, O, and S; mono- or bicyclic aryl-C<sub>1</sub>-C<sub>6</sub>-alkyl, mono- or bicyclic heteroaryl-C<sub>1</sub>-C<sub>6</sub>-alkyl, -S(=O)<sub>2</sub>-(CH<sub>2</sub>)<sub>1-6</sub>-R<sup>11</sup>, -C(=O)R<sup>11</sup>, -S(=O)<sub>2</sub>-(CH<sub>2</sub>)<sub>2-6</sub>R<sup>12</sup>, and -C(=O)-(CH<sub>2</sub>)<sub>1-6</sub>-R<sup>12</sup>; wherein R<sup>11</sup> and R<sup>12</sup> are as defined above;

R<sup>15</sup> and R<sup>16</sup> are selected from the group listed above for R<sup>9</sup>, R<sup>10</sup>, and R<sup>13</sup>, and are further selected from the group consisting of hydroxy, C<sub>1</sub>-C<sub>6</sub>-alkyloxy, aryloxy, heteroaryloxy, thio, C<sub>1</sub>-C<sub>6</sub>-alkylthio, C<sub>1</sub>-C<sub>6</sub>-alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub>-alkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, amino, mono- or di-C<sub>1</sub>-C<sub>6</sub>-alkylamino, mono- or diarylamino, mono- or diheteroarylamino, N-alkyl-N-arylamino, N-alkyl-N-heteroarylamino, N-aryl-N-heteroarylamino, aryl-C<sub>1</sub>-C<sub>6</sub>-alkylamino, carboxylic acid, carboxamide, mono- or di-C<sub>1</sub>-C<sub>6</sub>-alkylcarboxamide, mono- or diarylcarboxamide, mono- or diheteroarylcarboxamide, N-alkyl-N-arylcarboxamide, N-alkyl-N-heteroarylcarboxamide, N-aryl-N-heteroarylcarboxamide, sulfonic acid, sulfonamide, mono- or di-C<sub>1</sub>-C<sub>6</sub>-alkylsulfonamide, mono- or diarylsulfonamide, mono- or diheteroarylsulfonamide, N-alkyl-N-arylsulfonamide, N-alkyl-N-heteroarylsulfonamide,

N-aryl-N-heteroarylsulfonamide, urea; mono- di- or tri-substituted urea, wherein the substituent(s) is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub>-alkyl, aryl, heteroaryl; O-alkylurethane, O-arylurethane, and O-heteroarylurethane; and

wherein the cyclically-constrained  $\gamma$ -amino acid residues are selected from the group consisting of:



wherein R, together with the carbons to which it is attached, and further together with the  $\beta$ -position carbon in the  $\gamma$ -amino acid backbone where appropriate, independently defines a substituted or unsubstituted, monocyclic or bicyclic C<sub>3</sub> to C<sub>10</sub> cycloalkyl, cycloalkenyl, or heterocycle moiety, the heterocycle moiety having 1, 2, or 3 heteroatoms selected from the group consisting of N, S, and O; and

each "Y" is independently variable and is a single bond or a reverse-turn moiety; and

each "A" is independently selected from the group consisting of hydrogen, hydroxy, an amino-terminus protecting group, and a carboxy-terminus protecting group; and

each "a," "c," and "d" is an independently variable positive integer, and wherein "a" + "c" > 3; and salts thereof.

7. (CANCELED)

8. (ORIGINAL) The compound of Claim 6, wherein at least one of X or Z is a cyclically-constrained  $\beta$ -amino acid residue wherein V and W, and the carbon atoms to

which they are bonded, define a substituted or unsubstituted C<sub>4</sub> to C<sub>6</sub> cycloalkyl, cycloalkenyl, or heterocyclic ring having one nitrogen atom as the sole heteratom.

9. (ORIGINAL) The compound of Claim 6, wherein at least one of X or Z is a cyclically-constrained  $\beta$ -amino acid residue wherein V and W, and the carbon atoms to which they are bonded, define a substituted or unsubstituted cyclopentyl, cyclohexyl, pyrrolidinyl, or piperdinyl ring.

10. (CANCELED)

11. (WITHDRAWN and PREVIOUSLY PRESENTED) A method of probing, disrupting, or mimicking binding interactions between two protein molecules or fragments thereof, the method comprising:

in an *in vivo*, *in vitro*, or *ex vivo* reaction between the two proteins,

- (a) introducing to the reaction an unnatural polypeptide compound according to Claim 3; and then
- (b) quantifying any effect of the added compound from step (a) on thermodynamic or kinetic parameters of the binding interaction between the two protein molecules or fragments thereof.

12-14. (CANCELED)